Summary

The role of Nrf2 in selected models of liver injury

Oxidative stress accompanies various forms of liver injury, including liver resection and toxic liver injury. Two-thirds partial hepatectomy (PHx) is an established model for the study of liver regeneration after resection. We tested the effect of epigallocatechin gallate (EGCG), a green tea antioxidant, on the early phase of liver regeneration after PHx. Male Wistar rats received either water for injections or EGCG for 3 consecutive days and then were subjected either to laparotomy or hepatectomy. We observed a lower accumulation of bromodeoxyuridine pointing to lower DNA synthesis in hepatectomized rats receiving EGCG in a dose of 50 mg/kg than in hepatectomized rats treated with water. The activity of caspases 3/7, expression of p-p53 and tissue levels of IL-6 displayed a similar trend. EGCG in a dose of 20 mg/kg had no such effects.

Next, male Wistar rats were subjected either to PHx or laparotomy. Twenty-four hours after the surgery, hepatocytes were isolated and treated with various concentrations of EGCG for 24 h. Morphological criteria, cell viability tests, and albumin synthesis revealed toxicity starting at 10 μmol/L. DNA synthesis was higher in hepatocytes isolated from rats after PHx and inhibited by EGCG. Furthermore, EGCG increased the activity of caspases 3 and 7, more in hepatocytes from rats after PHx.

In the second part of our study, we investigated the association between apolipoprotein E (ApoE) genotype and susceptibility of mice hepatecytes to the toxicity of acetaminophen (APAP). Recently, an association between ApoE genotype and Nrf2 expression was described. Nrf2 is a transcription factor, important for combating oxidative stress in the liver and other organs and detoxification of hepatotoxic drugs, including APAP. We compared the toxicity of APAP on primary culture hepatocytes isolated from transgenic mice carrying two different human ApoE alleles, ApoE3 or ApoE4, and wild-type (WT) controls. APAP led to a dose-dependent hepatotoxicity in all strains tested, least in WT mice and most in ApoE3 mice. Concurrently, there was a decline in mitochondrial membrane potential, especially in ApoE3 hepatocytes. The formation of reactive oxygen species after 24 hour incubation with 2.5 mM APAP was most increased in hepatocytes of the ApoE3 genotype. Caspases 3 and 7 were not activated upon APAP treatment. We observed higher lipid accumulation in hepatocytes isolated from both transgenic strains than in WT controls. The expression of Nrf2-dependent genes was higher in ApoE3 than in ApoE4 hepatocytes.